Abstract

Chronic myeloid leukemia is a clonal haematopoietic disease, with characteristic BCR-ABL1 fusion gene. Despite the significant improvement in patient treated with tyrosine kinase inhibitors (TKI), 20–30 % of patients develop resistance. One of the main causes of treatment failure are mutations in the BCR-ABL1 kinase domain (KD). The aim of this work was to elucidate the molecular mechanisms of resistance and mutagenesis development in CML using an in vitro CML model KCL-22. The main part of this work was focused on the identification of genes involved in DNA damage response and repair, that could play a role in the process of mutagenesis of BCR-ABL1. We used the RT2 Profiler PCR Arrays method for the group of selected genes regulating DNA damage response and repair. We identified the genes XRCC6 and PARP1 whose gene expression was significantly and specifically decreased during KD BCR-ABL1 mutagenesis. Products of these genes are involved in repairing DNA double-strand breaks through non-homologous end joining (NHEJ). During study of the KD BCR-ABL1 mutagenesis we also found that clones, which developed mutations, did not show the increased BCR-ABL1 expression in the beginning of the culture compared to the clones in which mutations have not evolved.

Key words: myeloid leukemia, mutation, resistance to TKI, gene expression, XRCC6, PARP1